



Is Annual Cumulative Susceptibility Test Data Enough to Guide Empirical Therapy for *Pseudomonas aeruginosa* Pneumonia?

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Abstract

Purpose: The purpose of this study was to assess whether annual reporting by CSTD is adequate information for providers to best select empiric antimicrobial agents for *Pseudomonas aeruginosa* pneumonia in hospitalized patients. Also, this work investigated the advantage of using anatomic-site susceptibility data and created a combination antibiogram to determine which two antipseudomonal agents would offer the broadest empirical coverage.

Methods: A retrospective analysis was done on hospitalized patients treated at Mayo Clinic Florida who had *P. aeruginosa* isolated from January 1, 2016, through December 31, 2016. All *P. aeruginosa* isolates were categorized by anatomical site (blood, urine, abdomen and pelvis, soft tissue and skin, lungs, and miscellaneous). Anatomical-site and CSTD analyses were used to determine percentage of *P. aeruginosa* isolates susceptible to various antimicrobials. The primary objective was to assess whether differences in reporting between anatomical-site and CSTD alter antibiogram susceptibilities percentages, and to determine which antimicrobial combination would provide the best empiric double coverage for *P. aeruginosa*. The primary objective was achieved by comparing the standard CSTD antibiogram to the anatomical-site antibiogram. Then, a combined susceptibility report of the two most commonly used agents at our institution, piperacillin tazobactam and ceftazidime with other agents was created in order to enhance the probability that the empiric coverage with an additional agent would offer inhibitory activity against *P. aeruginosa* with at least one of the two agents.

Results: CSTD showed that 90% of all *P. aeruginosa* isolates were susceptible to ceftazidime, but anatomical site data showed that only 85% of pulmonary isolates were susceptible. CSTD showed that 90% of all isolates were susceptible to piperacillin tazobactam, but anatomical site data showed that only 87% of pulmonary isolates were susceptible to piperacillin tazobactam. Anatomical site susceptibility data showed that more than 10% of *P. aeruginosa* isolates from pulmonary specimens were resistant to piperacillin tazobactam and ceftazidime. When combined with piperacillin tazobactam or ceftazidime, aminoglycosides showed the greatest inhibition of isolates obtained from patients with suggested *P. aeruginosa* pneumonia.

Conclusion: Reporting anatomical site data for *P. aeruginosa* and combination antibiograms, in addition to CSTD, provide improved guidance for empirical therapy against *P. aeruginosa*.

Keywords: Anatomical site antibiogram; Antimicrobial stewardship programs; Combination antibiogram; Data stratification; *Pseudomonas aeruginosa* pneumonia empirical therapy

Abbreviations

ATS: American Thoracic Society; CLSI: Clinical and Laboratory Standards Institute; CSTD: Cumulative Susceptibility Test Data; IDSA: Infectious Diseases Society of America

Introduction

Antibiograms and Cumulative Susceptibility Test Data (CSTD), as reported by microbiology laboratories, are minimum requirements for antimicrobial stewardship programs. Empiric

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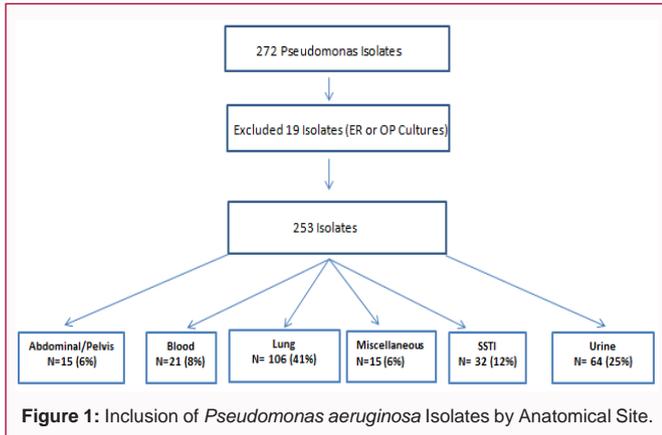


Figure 1: Inclusion of *Pseudomonas aeruginosa* Isolates by Anatomical Site.

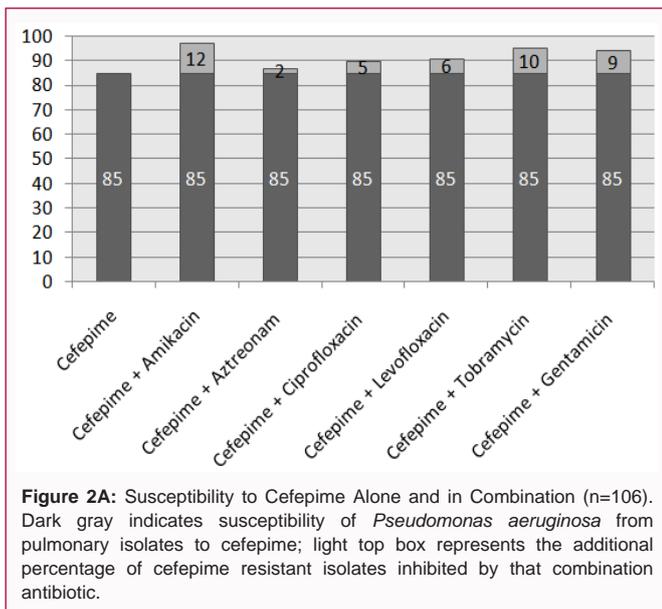


Figure 2A: Susceptibility to Cefepime Alone and in Combination (n=106). Dark gray indicates susceptibility of *Pseudomonas aeruginosa* from pulmonary isolates to cefepime; light top box represents the additional percentage of cefepime resistant isolates inhibited by that combination antibiotic.

antimicrobial therapies are guided by various factors, including local resistance patterns of commonly isolated bacteria. Microbiology laboratories typically provide CSTD to health care providers. The Clinical and Laboratory Standards Institute (CLSI) recommends reporting CSTD at least annually [1,2]. However, data stratification has been proposed as a method to optimize empirical therapy regimens [3].

Pseudomonas aeruginosa causes many serious nosocomial infections, including pneumonias, which are associated with marked morbidity and mortality [4]. Selection of appropriate treatment is a challenge, and use of empirical combination therapy to treat *P. aeruginosa* and other gram-negative bacterial infections is justified to expand the spectrum of drug activity, promote synergy, and potentially prevent resistance [5]. Unquestionably, the properly selected combination of agents broadens the spectrum of drug activity and increases the odds that 1 of the agents has *in vitro* activity against the pathogen, especially if the combination is determined on the basis of local susceptibility data. Use of combination antimicrobial therapy has been incorporated into current national guidelines for treatment of hospital-acquired pneumonia [6]. The 2016 guidelines of the Infectious Diseases Society of America (IDSA) for hospital-acquired and ventilator-associated pneumonia suggest prescribing antipseudomonal agents from different classes of antibiotics as an

empirical treatment strategy if a patient has any of the following [7]: 1) the patient has risk factor(s) for multidrug-resistant pathogens; 2) the patient is in a unit where more than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy; 3) the patient is in an intensive care unit for which antimicrobial susceptibilities are not available [8]. Therefore, an institutionspecific antibiogram in conjunction with an anatomical site antibiogram offers a provider a profile of resistance patterns at specific anatomical sites that might not be detected with CSTD. CSTD would be sufficient data for providers provided that there is not greater than 10% resistance among *P. aeruginosa* for a given anatomical site, such as lungs. When greater than 10% resistance for *P. aeruginosa* at a given anatomic site is detected, finding the best combination of inhibitory agents for empiric use may be beneficial.

Methods

The Mayo Clinic Institutional Review Board approved this study. Mayo Clinic Florida is a University affiliated 304 bed hospitals. Our institutions clinical microbiology database (SoftLabMic; SCC Soft Computer) was queried to identify patients hospitalized at our institution with *P. aeruginosa* isolates obtained from January 1, 2016, through

December 31, 2016. Isolates obtained from the emergency department and outpatient settings were excluded from the data set. Only diagnostic isolates were included; isolates from surveillance screening cultures and non-patient sources were excluded.

Conventional Micro Scan panels (Dried Gram-Negative MIC/ Combo Panels; Beckman Coulter Inc.) were inoculated with fresh organism isolated from samples with the Prompt Inoculation System (Becton, Dickinson and Co) and incubated at 35°C in ambient air for 24 hours. Organisms were identified with the biochemical substrates in the panel, which resulted in a score that was then compared with scores in the Micro Scan Walk Away system (Beckman Coulter Inc.). For each organism, antimicrobial susceptibility was determined by comparing the minimum inhibitory concentration (the lowest antimicrobial concentration that inhibited growth) with the appropriate CLSI range for each organism-drug combination identified with the Micro Scan Walk Away System (Beckman Coulter Inc) software.

Data about the isolates were compiled and stratified by anatomical site. Only anatomical sites with antimicrobial susceptibility data for at least 30 organisms were used in this study. The anatomical sites of the *P. aeruginosa* isolates were categorized as blood, urine, abdomen and pelvis, soft tissue and skin, lungs, and miscellaneous cultures (sinus, laryngeal, and port tip cultures). Susceptibilities to cefepime and piperacillin tazobactam (the most common monotherapeutic agents used to treat *P. aeruginosa* at our institution) were compared by using CSTD and anatomical site data for *P. aeruginosa*. CSTD for *P. aeruginosa* were compiled according to CLSI breakpoints [1-4].

The pulmonary source was the only anatomical site that had greater than 10% resistance to Piperacillin tazobactam and Cefepime, two agents that could be considered for monotherapy for *P. aeruginosa*.

Piperacillin tazobactam and Cefepime by anatomical site had a susceptibility rate of 87% and 85% respectively vs. 90% by CSTD for both antimicrobial agents. The percentage of *P. aeruginosa* isolates that were susceptible to amikacin, aztreonam, ciprofloxacin,

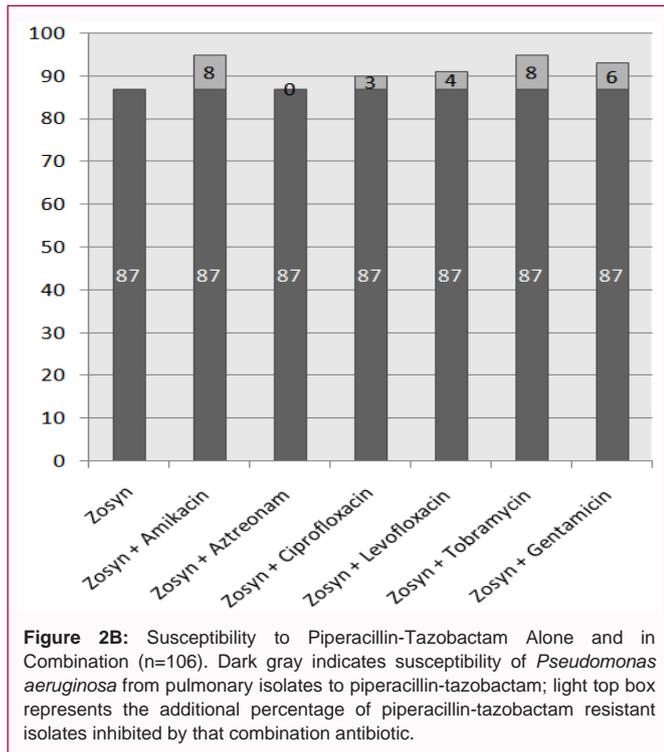


Figure 2B: Susceptibility to Piperacillin-Tazobactam Alone and in Combination (n=106). Dark gray indicates susceptibility of *Pseudomonas aeruginosa* from pulmonary isolates to piperacillin-tazobactam; light top box represents the additional percentage of piperacillin-tazobactam resistant isolates inhibited by that combination antibiotic.

levofloxacin, tobramycin, and gentamicin were then calculated to find the potential added benefit one would receive by adding on one of these agents when resistant to *P. aeruginosa* was found. The primary objective of the study was to use *P. aeruginosa* isolates to assess whether differences in reporting between anatomical site data and CSTD alter antibiogram susceptibility percentages. The secondary objective was to prepare a combination antibiogram for evaluation of *P. aeruginosa* at our institution.

Results

In total, 272 *P. aeruginosa* isolates were obtained from hospitalized patients at our institution. Nineteen isolates were excluded because they were obtained at the emergency department or outpatient settings. Therefore, 253 isolates were included 25 (9.8%) isolates from ICU and 228 (90%) from regular units: 106 (42%) from the lungs; 21 (8%), blood; 64 (25%), urine; 32 (13%), skin and soft tissue; 15 (6%), abdominal and pelvis; and 15 (6%), miscellaneous sources (Figure 1). CSTD showed that cefepime and piperacillin tazobactam inhibited 90% of *P. aeruginosa* isolates (Table 1). The percentages of *P. aeruginosa* isolates susceptible to cefepime (90%) and piperacillin tazobactam (90%) were both higher according to CSTD than according to anatomical site for the lungs (85% and 87%,

respectively). Ciprofloxacin inhibited 78% of isolates; levofloxacin, 80%; and aztreonam, 71%.

When cefepime was used in combination with amikacin, aztreonam, ciprofloxacin, levofloxacin, tobramycin, or gentamicin, the inhibitory activity against lung isolates was higher than when cefepime was used alone (Figure 2A). Similarly, when piperacillin tazobactam was used in combination with these antibiotics, the combined inhibitory activity was higher (with the exception of aztreonam) than when piperacillin tazobactam was used alone (Figure 2B). Aminoglycosides-amikacin, tobramycin, and gentamicin-provided the greatest additional inhibition of *P. aeruginosa* isolates acquired at our institution when used in combination with empirical cefepime or piperacillin tazobactam.

Discussion

Antibiograms and CSTD are mainly used 1) to guide empirical antibiotic selection until a pathogen with specific susceptibilities is isolated and 2) to track resistance patterns. Several epidemiologic studies have shown that empirical antimicrobial administration increases hospital mortality rates when antibiotic treatment of hospital-acquired pneumonia is inadequate [8,9]. Pathogens associated with high resistance rates, including *Pseudomonas* species, *Serratia* species, *Enterobacter* species and *Acinetobacter* species [10], are major concerns. For this reason, *P. aeruginosa* was chosen to determine whether reporting by anatomical site-specific antibiograms alters antibiogram susceptibility percentages and potentially improves empirical antimicrobial selection for *P. aeruginosa* at our institution. CSTD and cumulative antibiograms are based on species-specific data for many isolates (2:30 isolates are required according to CLSI guidelines) and report the percentage susceptible to a given antimicrobial agent [11]. CSTD, as typically reported by microbiology laboratories, may blur differences related to the source of the isolate, such as anatomical site, unit location, and patient population. The potential pitfalls of combining data for all tested isolates into 1 hospital-wide antibiogram have been reported [3]. We determined that reporting anatomical site antimicrobial susceptibility data, in addition to CSTD, altered recommendations for empirical antimicrobial therapy for *P. aeruginosa* at our institution. By using anatomical site reporting, we determined that the inhibitory activities of the monotherapeutic agents commonly used at our institution may be suboptimal according to the American Thoracic Society (ATS) and IDSA guidelines for the management of *P. aeruginosa* pneumonias [6]. CSTD for our study indicated that cefepime and piperacillin tazobactam inhibited 90% of *P. aeruginosa* isolates. However, susceptibility results for pulmonary anatomical site data were lower for cefepime and piperacillin tazobactam compared with CSTD for isolates with greater than 10% resistance.

Table 1: Percentages of *Pseudomonas aeruginosa* isolates susceptible to antimicrobials by anatomical site in 2016.

Anatomical Site	Aztreonam	Ciprofloxacin	Levofloxacin	Cefepime	Piperacillin-Tazobactam	Gentamicin	Amikacin	Tobramycin
Abdomen and pelvis (n= 15)	86	53	53	100	100	80	100	100
Blood (n=21)	66	80	80	90	90	90	95	100
Lungs (n= 106)	71	78	80	85	87	82	87	91
Skin and soft tissue (n=32)	81	84	84	90	96	93	100	93
Urine (n=64)	78	79	78	95	92	85	96	96
Miscellaneous (n= 15)	86	86	86	100	93	93	100	100
Cumulative susceptibility test data (N=253)	75	78	79	90	90	85	93	94

By using only CSTD data, one could assume that dual therapy for *P. aeruginosa* is not warranted because resistance was not greater than 10%; however, when *P. aeruginosa* was analyzed by anatomical site, 15% of isolates from pulmonary sources were resistant to cefepime and 17% were resistant to piperacillin tazobactam. This discrepancy was detected when *P. aeruginosa* data were stratified by anatomical site. Therefore, if a clinician suspects that a patient has *P. aeruginosa* pneumonia, dual or combination antimicrobial therapy should be considered at our institution. Anatomical site data showed that 15% of *P. aeruginosa* isolates from the lungs were resistant to cefepime and 13% were resistant to piperacillin tazobactam. According to these data, hospitalized patients with probable *P. aeruginosa* pneumonia may benefit from receiving empirical dual antimicrobial therapy, for example, a P-lactam antibiotic and an antibiotic from a different class, until cultures are finalized. Reporting combination antibiograms to guide empirical therapy for *P. aeruginosa* infection is not standard practice in the United States, but this has been proposed [12,13]. After we determined the inhibitory activity of cefepime and piperacillin tazobactam against each *P. aeruginosa* isolate, we determined the inhibitory activity against pulmonary isolates when other antimicrobials were added in combination. We determined that the amino glycoside class of antibiotics had the greatest inhibitory activity when co administered with cefepime and piperacillin tazobactam (all-lactams) to isolates from hospitalized patients with suggested *P. aeruginosa*. The addition of an amino glycoside broadens the antibacterial spectrum, which may reduce the risk of inadequate empirical therapy. However, the addition of amino glycosides is controversial [14,15], and their use in the empirical treatment of sepsis increases the risk of adverse effects, including nephrotoxicity [16]. Therefore, clinical microbiology laboratories may need to stratify data by anatomical site, to at least identify whether the site is pulmonary, in addition to providing cumulative antibiograms. We recommend the use of combination antibiograms for infections associated with multidrug-resistant pathogens when empirical combination therapy is being considered. Limitations to our study include the retrospective nature of the study. For example, a culture could have been drawn on a medical ward prior to transferring the patient to the ICU thereby making our percentage of ICU vs. non-ICU cultures inaccurate.

Conclusion

Reporting anatomical site antibiograms along with CSTD allows providers to discern if dual antimicrobial therapy at one's institution is indicated, especially for *P. aeruginosa* pneumonia. We found that the reporting of just CSTD hid an opportunity for us to utilize 2 antimicrobials, as advised by ATS/IDSA to improve our initial management of these pneumonias. The creation of a combination antibiogram based on anatomical site further clarified which agents (in our case aminoglycosides) added the most too inhibitory activity with piperacillin tazobactam or cefepime for empiric therapy for *P. aeruginosa*.

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